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MEETING ABSTRACTS Open Access

The HIV nef protein within ARL is genetically and structurally distinct from those in the brain of patients with HAD

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Background

Despite antiretroviral therapy, macrophages remain significant cellular reservoirs for HIV infection. Two fatal macrophage-mediated diseases still occur at a much higher rate in the HIV-infected and HAART-treated population: (1) AIDS-related lymphoma (ARL), a noninflammatory disease, and (2) HIV-associated dementia (HAD), an inflammatory disease. The frequency of HIV-infected macrophages in ARL is 50%. Macrophages are the primary HIV-infected cells in the brain. The mechanisms that lead to the development of these diseases are not understood. Because certain subtypes of HIV are associated with a higher prevalence of HAD, a viral genetic determinant for HAD development is likely. On the other hand, ARL development occurs fairly consistently across multiple HIV subtypes and genetic analysis has clearly differentiated ARL tissue-associated HIV from non-ARL tissue HIV within individuals. These facts raise two questions: (1) Are there tumor-specific genetic differences among HIV proteins that could influence the macrophage to accelerate ARL development? (2) How might HAD-associated and ARL-associated viruses differ at the genetic and structural levels? Our goal was to analyze HAD and ARL viral sequences and determine whether a disease association could be identified within viral proteins.

Methods

The AIDS and Cancer Specimen Resource (ACSR) archives tissue samples derived from well-documented cases of both ARL and HAD. Multisite autopsies of 7 patients with ARL, HAD, and other neurological and systemic disorders were identified at the ACSR. More than 20 sequences from each of 5 to 7 tissues from each patient were sequenced. The HIV nef sequence was used in multiple genetic analyses, including a neural net signature pattern analysis, a tertiary structural analysis, and an analysis of the stability of an HIV viral microRNA associated with apoptosis.

Results

Signature pattern analysis clearly separated ARL from HAD viruses and identified positions that may in concert produce specific pathological outcomes. HIV subtype D viruses are known to be associated with a high rate of HAD. Comparative tertiary structural analysis of nef showed that HAD viruses were more similar to HIV subtype D viruses than ARL viruses. ARL viruses were either missing or possessed a less stable miR-H1 structure compared to HAD viruses.

Conclusions

Our results show that HIV-associated diseases are likely related to specific viral genetic signatures and structures. Discovery of an ARL virus would enable the development of diagnostic tools and identify subsets of viruses to be targeted with drugs or vaccines.

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